Malignancy-associated hypercalcemia in children: A Systematic Review

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Online Resource 1: Supplementary Material

Supplementary Table S1: PubMed/MEDLINE search strategy

(((((("Infant"[Mesh]) OR ("Child"[Mesh])) OR ("Adolescent"[Mesh])) OR (Pediatric*[Title/Abstract])) AND ((((cancer*[Title/Abstract]) OR (malignan*[Title/Abstract])) OR (leukemia*[Title/Abstract])) OR (lymphoma*[Title/Abstract])))) AND ((("Hypercalcemia"[Mesh]) OR (hypercalcemia[Title/Abstract])) OR (hypercalcaemia[Title/Abstract])).

Supplementary Table S2: Clinical characteristics of case reports on pediatric malignancy-associated hypercalcemia in hematological malignancies

Study	**Underlying malignancy**	**Sex (F/M)**	**Age (y)**	**Peak calcium (mg/dL)**	**Timing**	**Mechanism**	**Management**	**Outcomes and resolution**
1 [1]	B-ALL	M	7	15.6	Dx	NR	Hydr+Diu+CTN+BP	Res (5d)
2 [2]	B-ALL	F	16	18.0	Dx	NR	Diu + CTN + BP	DOD
3 [3]	B-ALL	M	11	13.8	Dx	NR	Diu + BP	Res (48h)
4 [4]	B-ALL	M	18mo	15.0	Dx	NR	Hydr+Diu	Res: hypoCa
5 [5]	B-ALL	M	4	19.2	Dx	OL + VitD	Hydr+Diu+BP	Res: hypoCa
6 [6]	B-ALL	M	3	16.5	Dx	NR	Hydr + BP	Res (2w)
7 [7]	B-ALL	M	2	21.2	Dx	OL	Hydr+ BP	Res post-chemo
8 [8]	B-ALL	F	6	14.9 Rel: 15.5	Dx + Rel	HHM	Hydr+Diu+CTN; Rel: +BP	Res both episodes; hypoCa (2^{nd}); DOD
9 [9]	B-ALL	F	14	15.55	Dx	NR	Hydr+Diu+BP	Res: hypoCa
10 [10]	B-ALL	F	9	16.3	Dx	Cyt	Hydr+Diu+BP	Ref; Res post-chemo
11 [11]	B-ALL	M	9mo	19.0	Dx	NR	Hydr+Diu+BP	Res post-chemo
12 [12]	B-ALL	F	9	18.7	Dx	HHM	Hydr+Diu+Ster+CTN	Res: hypoCa
13 [13]	B-ALL	F	14	16.8 Rel: 18.6	Dx + Rel	PTHrP	Hydr+BP+CTN	Res (2d); Rel: Res post-chemo; DOD
14 [14]	B-ALL	M	12	19.0	Dx	OL	Diu+BP+CTN	Res: hypoCa
15 [15]	B-ALL	M	2	15.8	Dx	Cyt	BP	Res; Rel
16 [15]	B-ALL	F	2	16.6	Dx	Cyt	BP	Res
17 [16]	B-ALL	M	11	12.9	DX	NR	Hydr+Diu	Res: hypoCa; DOD
18 [17]	B-ALL	F	4	14.0	Prog	NR	Hydr+Diu+Ster	Res; DOD (rec hyperCa)
19 [18]	B-ALL	M	6	17.0	Dx	NR	Hydr+Diu+BP+Ster+HD	Res

20 [19]	B-ALL	M	1	13.2	Dx	NR	NR	NR
21 [19]	B-ALL	F	1	10.6	Dx	NR	NR	NR
22 [20]	B-ALL	F	8	15.5	Rel	PTHrP	Hydr+Diu+Ster+BP+CTN	Res (3d)
23 [21]	B-ALL	F	4	13.3	Dx	NR	Hydr+Diu+BP+CTN	Res post-chemo
24 [22]	B-ALL	M	11	15.0 Rel: 16.0	Dx + Rel	PTHrP	Hydr+Diu+BP+Ster	Res (1w): HypoCa
25 [23]	B-ALL	M	3	18.64	Dx	OL	Hydr+Diu+ster	Res post-chemo; DOD
26 [24]	B-ALL	M	7	12.6	Dx	NR	Hydr+Diu	Res (72h)
27 [25]	B-ALL	M	10	14.2	Dx	OL	Hydr+Diu+BP	Res (48h)
28 [26]	B-ALL	M	3	21.8	Dx	NR	Hydr + CVVHD + BP	Res: HypoCa
29 [27]	B-ALL	F	14	13.0	Dx	NR	Hydr	NR
30 [28]	B-ALL	M	5	19.5	Dx	NR	Hydr+Diu+CTN+BP	Res (±chemo)
31 [29]	B-ALL	M	12	19.0	Dx	HHM	Hydr+Diu+Ster+BP	Res (72h); HypoCa
32 [30]	B-ALL	M	17	19.4	Dx	NR	NR	DOD
33 [31]	B-ALL	M	5	20.2	Dx	NR	Hydr+Deno	Res (36h); HypoCa
34 [32]	B-ALL	M	3	15.0	Dx	NR	Hydr+Diu+ster	Res (5d)
35 [33]	B-ALL/lym.	M	13	>13.99	Dx	OL	Hydr+Diu+CTN+BP	Res (3d); HypoCa
36 [34]	ALL	M	10	16.23	Dx	NR	Hydr+Diu+HM+BP	Res: HypoCa
37 [35]	ALL	F	9	11.5	Dx	NR	CTN	Res (14d)
38 [36]	ALL	F	12	16.8	Dx	PTH	Surg +chemo	Res
39 [37]	ALL	M	3	16.0	Dx	NR	Hydr+Diu+ster	Res; DOD
40 [38]	ALL	M	9	18.44	Dx	OL	Diu+CTN+ HD	Res; DOD
41 [39]	ALL	F	8	20.0	Dx	OL	Hydr+Diu+BP+CTN	Res (3d): HypoCa
42 [40]	ALL	F	14	15.6	Dx	NR	Hydr+Diu+BP+CTN	Res (24h)
43 [41]	ALL	F	6	14.1	Dx	NR	Hydr+BP	Res
44 [42]	ALL	M	7	12.4	Dx	PTHrP	Hydr+Diu	Res post-chemo
45 [43]	ALL	F	15	14.4	Dx	ePTH	Hydr+Diu+Mith	Res; DOD
46 [44]	ALL	M	2	11.8	Dx	NR	Hydr+Diu+BP	Res
47 [45]	ALL	M	16	15.6	Dx	NR	Hydr+Diu+BP	Res
48 [46]	ALL	M	9	19.0	Dx	NR	Hydr+BP	Res; DOD
49 [46]	ALL	M	8	12.26	Dx	NR	BP	Res
50 [47]	ALL	F	5	17.3	Dx	NR	Hydr+Diu+BP	HypoCa; Res post-chemo
51 [48]	ALL	M	35mo	13.92	Dx	NR	Chemo	Res (18d)
52 [49]	ALL	M	3	13.0	Dx	PTHrP	Hydr+Diu+BP	Res: Hypoca
53 [50]	ALL	F	22mo	13.7	Dx	PTHrP	NR	Res post-chemo
54 [51]	ALL	M	6	14.4	Dx	HHM	Hydr+Diu+BP+CTN	Res (24h); HypoCa

55 [52]	ALL	F	3	18.2	Dx	ePTH	Hydr+Diu+Ster	Res (5d);
56 [53]	T-ALL	M	5	15.3	Dx	NR	Diu+Ster	DOD
57 [54]	T-ALL	F	8	20.0	Dx	PTHrP	Hydr+Diu+BP+CTN	Res
58 [55]	T-ALL	M	3	22.2	Dx	NR	Hydr+Diu+BP+CTN	Ref; Res post-chemo
59 [56]	AML	M	14	18.7	Dx	OL	Ster	Rec (3mo)
60 [57]	AML	F	14mo	18.44	Dx	PTHrP + Cyt	Hydr+Diu+BP	Res (2d)
61 [58]	NHL	M	4	18.9	Dx	NR	Hydr+Diu+BP+CTN+Ster	Res
62 [59]	HL	M	15	11.6	Dx	VitD	Chemo	Res
63 [60]	BL	M	12	14.4	Dx	NR	Hydr+Diu	Res; Chemo: HypoCa
64 [61]	BCL	M	4	15.0	Post-Tx	VitD	Hydr+Diu+CTN+Mith	Ref; Res post-surg; DOD
65 [62]	AMKL	F	2	15.23	Rel	NR	Hydr+Diu+Mith	Res (4d); DOD
66 [63]	AMKL	M	8mo	13.6	Dx	OL	Hydr+Diu+BP+CTN	+ Chemo: Res
67 [64]	AMKL	F	18mo	19.5	Dx	PN	Hydr+Diu+BP	Res: HypoCa; DOD
68 [65]	LBL	F	11	13.0	Rel	PTHrP	NR	DOD
69 [66]	Lym.	F	9	16.1	Dx	NR	Hydr+Diu+Mith	Res (24h)
70 [66]	Lym.	M	13	18.5	Dx	NR	Hydr+Diu+Mith+Ster	Res
71 [67]	MS + AML	F	6	16.55	Dx	NR	Hydr+Diu+CTN	Res

Abbreviations: ALL, acute lymphoblastic leukemia; Lym, lymphoma; AML, acute myeloid leukemia; HL, Hodgkin lymphoma; BL, Burkitt lymphoma; BCL, B-cell lymphoma; AMKL, acute megakaryocytic leukemia; LBL, lymphoblastic lymphoma; MS, myeloid sarcoma; NR, not reported; Dx, at diagnosis; Rel, at relapse; Prog, at progression; Rec, recurrence; Post-Tx, after transplant; OL, osteolytic-mediated; VitD, calcitriol-mediated; HHM, humoral hypercalcemia of malignancy; Cyt, cytokine-mediated; PTHrP, PTHrP-mediated; PTH, PTH-mediated; ePTH, ectopic PTH; PN, paraneoplastic; Hydr, hydration; Diu, diuretics; CTN, calcitonin; BP, bisphosphonate; Ster, corticosteroid; HD, hemodialysis; Chemo, chemotherapy; Deno, Denosumab; Surg, surgery; Mith, mithramycin; CVVHD, continuous venovenous hemodialysis; Res, resolution of hypercalcemia; DOD, died of disease; HypoCa, hypocalcemia; HyperCa, hypercalcemia; Res post-chemo, resolution after chemotherapy; Ref, refractory; Res post-surg, resolution after surgery.

Supplementary Table S3: Clinical characteristics of case reports on pediatric malignancy-associated hypercalcemia in solid tumors

Study	**Underlying malignancy**	**Sex (F/M)**	**Age**	**Peak calcium (mg/dL)**	**Timing**	**Mechanism**	**Management**	**Outcomes and resolution**
1 [68]	RMS	F	15	13.8	Prog	PTH	Hydr+Diu+CTN+Mith	Rec; DOD
2 [68]	RMS	F	12	15.0	Dx	PTH	Hydr+Diu+CTN+Ster	Rec
3 [69]	RMS	F	4	15.3	Dx	OL	Hydr+Diu+BP+CTN	Res (14d); DOD
4 [70]	RMS	M	14	15.91	Dx	ePTH	Hydr+Diu+BP	Rel;
5 [71]	RMS	M	17	15.1	Rel	ePTH	Hydr+Diu+BP+Deno	Res: HypoCa; DOD
6 [72]	RMS	M	17	16.2	Dx	NR	Hydr+BP+CTN	Res (6d); DOD

7 [73]	HB	F	6	14.2	Dx	PTHrP	CTN	Res post-surg
8 [74]	MRT	F	0m	12.42	Prog	PN	Chemo	DOD
9 [75]	MRT	M	6mo	21.6	Prog	ePTH	Hydr+Diu+ASA+Mith	Res; DOD
10 [76]	MRT	M	17mo	23.8	Dx	PTHrP	Surg	Res; DOD
11 [77]	ODG	F	13	12.9	Dx	HHM	BP+CTN	Res
12 [78]	ODG	F	14	15.0	Dx	PTHrP	Hydr+Diu+BP+CTN	Ref; Res post-surg
13 [79]	ODG	F	10	15.8	Dx	VitD	Hydr+Diu	Res post-surg
14 [80]	ODG	F	13	14.9	Dx	Unk	Hydr+Diu	Res post-surg (14d)
15 [80]	ODG	F	10	15.11	Dx	NR	Hydr+BP	Res post-surg
16 [81]	ODG	F	9	14.5	Dx	Unk	Hydr+Diu	Res post-surg
17 [82]	ODG	F	16	15.4	Dx	Unk	Hydr+Diu	Res post-surg
18 [83]	IFS	M	7mo	22.6	Dx	PTHrP	Hydr+Diu+Ster	Res; DOD
19 [84]	IFS	F	0m	16.9	Dx	PTHrP	Hydr+Diu	Res post-chemo
20 [85]	IFS	F	0m	15.6	Dx	PTHrP	Hydr+Diu	Res post-chemo
21 [85]	IFS	M	0m	19.0	Dx	PTHrP	Hydr+Diu	Res post-chemo
22 [86]	SCCO	F	10	13.0	Dx	NR	Surg + chemo	DOD
23 [86]	SCCO	F	15	15.2	Dx	NR	Surg+ chemo	Rel
24 [87]	SCCOHT	F	16	14.3	Rel	NR	NR	NR
25 [87]	SCCOHT	F	14	13.5	Dx	NR	Surg	Res; DOD
26 [87]	SCCOHT	F	13	17.0	Dx	NR	Surg	Res; Rec
27 [87]	SCCOHT	F	14	Elev	Dx	NR	Surg	Rec; DOD
28 [88]	SCCOHT	F	8	17.19	Dx	NR	Surg	Res
29 [89]	SCCOHT	F	17	11.2	Dx	PTHrP	Surg	Res
30 [90]	SCCOHT	F	15	19.2	Dx	NR	Hydr+ BP	Res post-surg; HypoCa
31 [91]	SCCOHT	F	10	11.82	Dx	NR	Surg	Res
32 [92]	SCCOHT	F	14	11.26	Dx	NR	Surg	DOD
33 [93]	SCCOHT	F	12mo	18.1	Dx	NR	Surg	Res
34 [94]	SCCOHT	F	10	12.34	Dx	PTHrP	Surg	Res post-surg; DOD
35 [95]	SCCOHT	F	16	17.3	Dx + Rel	PTHrP	Chemo + surg	Res; Rel: DOD
36 [96]	MPNST	M	5d	22.5	Dx	PTHrP	Hydr+Diu+CTN+BP+HM+ CVVHD	Res; DOD
37 [97]	Lung SqCC	M	16	13.9	NR	HHM	NR	Ref; Surg; DOD
38 [98]	Skin SqCC	M	5	12.8	Dx	VitD	Hydr+Diu+BP+Ster	Res (24h)
39 [99]	HepSar	M	3mo	13.8	Dx	PTHrP	Hydr+Diu	Ref; DOD

40 [100]	NPC	F	10	23.0	Dx	HHM	Hydr+Diu+BP	Res (11d); DOD
41 [101]	PGL	M	15	12.9	Dx	PTHrP	Hydr+Diu+CTN+BP	Res (± surg)
42 [102]	CCS	M	15	15.5	Dx	NR	Hydr+CTN+BP+Ster	DOD
43 [103]	NUT carcinoma	F	11	12.8	Dx	NR	CTN+BP	DOD
44 [104]	PRL	M	14	17.0	Dx	VitD	Hydr+CTN+BP	Res
45 [105]	SS	M	16	23.0	Dx	PTHrP	Hydr+CTN+BP	Res
46 [106]	RS	M	5	13.63	Dx	NR	Surg	Res; DOD

Abbreviations: RMS, rhabdomyosarcoma; HB, hepatoblastoma; MRT, malignant rhabdoid tumor; ODG, ovarian dysgerminoma; IFS, infantile fibrosarcoma; SCCO, small cell carcinoma of the ovary; SCCOHT, small cell carcinoma of the ovary, hypercalcemic type; MPNST, malignant peripheral nerve sheath tumor; SqCC, squamous cell carcinoma; HepSar, hepatic sarcoma; NPC, nasopharyngeal carcinoma; PGL, paraganglioma; CCS, clear cell sarcoma; NUT carcinoma, nuclear protein in testis carcinoma; PRL, primary renal lymphoma; SS, synovial sarcoma; RS, renal sarcoma; NR, not reported; Unk, unclear; Elev, elevated; Dx, at diagnosis; Rel, at relapse; Prog, at progression; Rec, recurrence; OL, osteolytic mediated; VitD, calcitriol-mediated; HHM, humoral hypercalcemia of malignancy; Cyt, cytokine-mediated; PTHrP, PTHrP-mediated; PTH, PTH-mediated; ePTH, ectopic PTH; PN, paraneoplastic; Hydr, hydration; Diu, diuretics; CTN, calcitonin; BP, bisphosphonate, Ster, corticosteroid; HD, hemodialysis; Chemo, chemotherapy, Deno, Denosumab; Surg, surgery; Mith, mithramycin; CVVHD, continuous venovenous hemodialysis; ASA, acetylsalicylic acid; Res, resolution of hypercalcemia; DOD, died of disease; HypoCa, hypocalcemia; HyperCa, hypercalcemia; Res post-chemo, resolution after chemotherapy; Ref, refractory; Res post-surg, resolution after surgery

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